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MEMORANDUM

Date: June 12, 1998

From: John C. Hill, Ph.D.

To: Kathleen A. Clouse-Strebel, Ph.D.

Through: David S. Finbloom, M.D.

Subject: CMC Review of BLA 980286, Immunex's TNFR:Fc for RA

I. INTRODUCTION

TNFR:Fc is a [redacted] dimerized form of TNFR produced in genetically engineered Chinese hamster ovary (CHO) cells. The cells that produce TNFR:Fc are cultured using proprietary media and fermentation methods and subsequently purified via a series of chromatography steps, a viral inactivation and viral filtration step. The Drug Product is a sterile, lyophilized powder, formulated with tromethamine (Tris), USP/NF; mannitol, USP/NF; and sucrose, USP/NF as excipients.

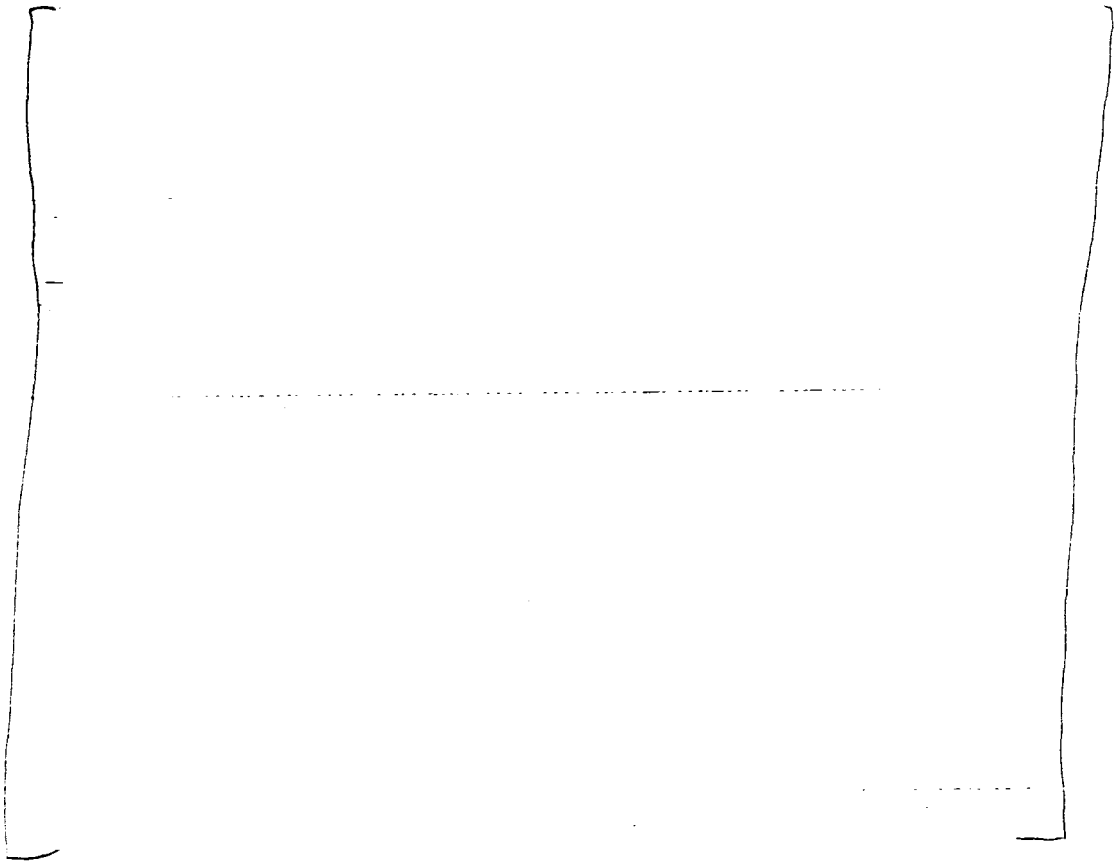
II. DRUG SUBSTANCE

A. Description and Characterization

1. Description

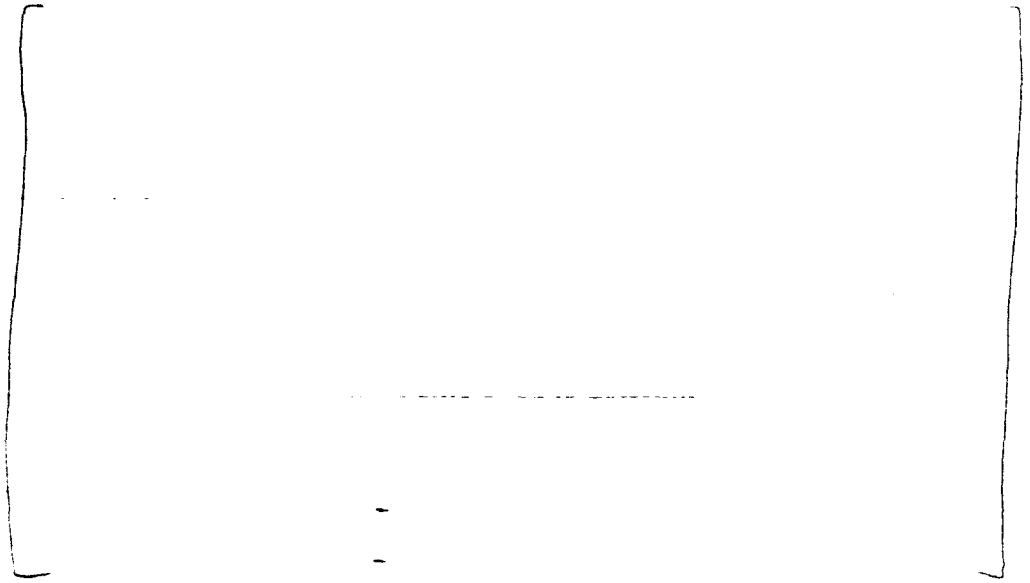
[(TNFR:Fc) is a [redacted] dimerized form of TNFR produced in genetically engineered Chinese hamster ovary (CHO) cells. TNFR:Fc consists of the extracellular domain sequence of TNFR (p75 TNF receptor) [redacted]

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)



2. Characterization / Proof of Structure

a. Physicochemical Characterization of Reference Standard and Qualifying Lots



[redacted]

These tests reflect historical through current attempts of the manufacturer to "fully characterize" the chemical nature of the TNFR:Fc molecule. Not all of the tests listed are utilized for lot release or qualification of reference standard lots. Additionally, not all of the tests have been used to demonstrate "comparability" between the various production scales.

Routine methods for the physicochemical characterization of Bulk Drug Substance have been selected following guidelines described in ICH Q6B "Specifications: Test Procedures and Accecptance Criteria for Biotechnological / Biological Products, Draft of Feb. 6, 1998". This testing is summarized as(8:12-13):

ICH Q6B Criteria (Section 4.0)	Test Method	Comment
Appearance/Description	[redacted]	Assay conforms to compendial guidance.
Identity	[redacted]	[redacted]
Purity and Impurities	[redacted]	[redacted]
Potency	[redacted]	[redacted]
Quantity	[redacted]	[redacted]
General Quality Assays	[redacted]	[redacted]
General Tests	[redacted]	Assays conform to compendial/regulatory guidance.
Safety	[redacted]	Assays conform to compendial/regulatory guidance.

b. Biological Activity

Description of the assay and data demonstrating bioequivalence for the various production scales are provided (3:90-96).

B. Manufacturer

Two sites are used to produce TNFR:Fc

Material used for the phase three clinical trials was manufactured at Immunex's corporate headquarters are located in Seattle, Washington. Immunex Corporation is the license applicant for this Biologics License Application (BLA) for TNFR:Fc and is currently a licensed manufacturing facility (License Number 1132) for manufacture of LEUKINE® (sargramostim).

Material used for commercial release is manufactured at a contract manufacturer, located in is responsible for the manufacture, storage and testing of TNFR:Fc Bulk Drug Substance (BDS). The facility operates under cGMP conditions and has been licensed as a multi-product facility in the United States (License Number . A written agreement between and Immunex describes all of the functions performed by

C. Method of Manufacture

1. Raw Materials and Reagents

Raw materials are presented in two divisions; those components required for cellular culture and production (4:32-134) and those components required for downstream purification (4:135-156).

Materials required for the cell culture process are tabulated (4:32-34), indicating the material part number, grade and supplier(s). Test methods (SOP's) and acceptance criteria are listed for these raw materials (4:108-134). Certificates of analysis are included for materials sourced from animals (4:36-106). Immunex has in place a plan for auditing suppliers as to the quality of all raw materials (4:107).

Materials required for the purification process are tabulated (4:135-137), indicating the material part number, grade and supplier(s). Test methods (SOP's) and acceptance criteria are listed for these raw materials (4:138-156).

2. Flow Charts

Two flow charts are provided which serve to graphically illustrate the manufacturing process.

a. The process of cell growth and harvesting has been illustrated (4:162). Additionally, fermentation process steps have been tabulated (4:158), indicating the location where the process occurs, method of transfer and references to the associated BLA sections. In-process monitoring parameters (SOP's and specifications) are also tabulated for cell expansion in ——— (4:159), cell expansion in the ——— (4:160), media exchange (4:161) and ——— fermentor harvest (4:161).

b. Steps in the purification process have been graphically represented (4:166). Additionally, process steps have been tabulated (4:163), indicating the location of processing steps, method of transfer and references to relevant BLA sections. In-process monitoring parameters (SOP's and specifications) are also tabulated for each processing step (4:164-165).

3. Detailed Description

a. Cell Source

Construction of ——— vector, cloning, preparation of cell banks (Master Cell Bank, Working Cell Bank, analysis of cell lines and viral testing are described (4:167-182, 5:1-80).

b. Cell growth and Harvesting

i. Cell expansion

Cells derived from the Manufacturer's Working Cell Bank are thawed and propagated for inoculum generation (SOP GF 9081). Operators record in the log book the number of vials removed, vial numbers, removal date, intended use and initials of individuals removing the vials. The culture is placed in a ——— flask and allowed to gently mix. The ——— is labeled with ——— number, lot number, seeding density, preparation date and operator's initials. The target viable cell density for inoculation is ——— cells/mL. Expected culture growth is in the range of ——— culture doublings per passage with cell viability remaining above ——— Cultures are maintained for ——— and then ———

The stock culture is maintained by [redacted] (SOP 9084). [redacted] is limited by the specified overall cultivation time which is [redacted] from thaw of the WCB to harvest of the production culture. Inoculum scale-up cultures are prepared from the [redacted] (SOP GF 10074). The TNFR:Fc inoculum train has been graphically represented (5:89).

Figure 4.2.3.3-1
Cell Growth and Harvesting

[redacted]

In order to scale-up the culture volume, the cells are subsequently cultivated in approximately [redacted] volumes using appropriate [redacted] vessels(SOP's GF 9085-9086). All operations involving [redacted] flasks are performed under [redacted] conditions. The inoculum train prior to reaching the [redacted] scale consists of scaling from [redacted] (SOP GF 9087) to [redacted] SOP GF 9088) [redacted] cultures. [redacted]

[redacted] The volume of [redacted] cultures used for the inoculation of the [redacted] varies based on the required volume to meet the target [redacted] Cells are [redacted] are the parameters used to determine [redacted] Cultures displaying [redacted] are usually selected for further scale up.

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)

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Substance is [redacted] into [redacted] vessels and may be stored at [redacted] C for up to [redacted] As required, based on inventory requirements, [redacted] TNFR:Fc Bulk Drug Substance may be subsequently [redacted]

ii. Batch Records

[redacted] qualification lots have been manufactured at the [redacted] scale [redacted] and [redacted] Included in the BLA filing is the batch record for the manufacture of TNFR:Fc lot 25007 (English translation, volume 9; German original, volume 10). Submitted are those records pertaining to the processing steps, records concerning the formulation of buffers are not included. For the batch record submitted there were no deviations reported.

There is no specification mentioned for the shelf life of either the [redacted] column or the [redacted] column or the filters. No mention is made of the number of times the columns and filters may be used (no validation data presented). This data was provided as a supplement in the final BLA filing (2:8-23). No data was provided for validation of the reuse of the filters.

D. Process Controls

1. In-process Controls

Numerous tables are provided which summarize the in-process controls in place for expansion of the WCB from [redacted] cultures ([redacted] (6:12-14) through [redacted] (6:14-15), [redacted] (6:17) to the final production scale [redacted] (6:15) and pre-harvest testing for viral contamination (6:5).

In-process monitoring of the purification process is summarized in tabular form for both process parameters (6:22) and product activity pools (6:23).

2. Process Validation

Process validation protocol BTP0651P *Process Validation of the TRFI-01 Manufacturing Process (BDS)* defines the samples, testing, and acceptance criteria for validating the TNFR:Fc BDS cell culture production, harvest, and purification processes. The purposes of the process validation studies were to demonstrate product equivalency and process scalability for TNFR:Fc BDS manufactured at [redacted] with TNFR:Fc BDS manufactured at Immunex. The studies which were conducted to validate the process are summarized (6:25). Validation data presented is from the 1997 [redacted] scale TNFR:Fc campaign, with the production

runs identified as 25001, 25002, and 25003. Additional data from production runs 25005 and 25007 is included for some validation studies.

The process has been validated for the removal of impurities [redacted]

(6:110-126) (7:37-61).

Trend analysis of the [redacted] scale materials has been used to facilitate process validation and to demonstrate consistency of manufacture at the various scales. This data analysis indicates that there is a consistency of manufacture at the [redacted] scale that was lacking at other production scales.

Yields have been determined for each step of the purification process and action limits have been established (7:73-76).

Table 4.2.4.2.3.10-1
Mass Balance Chart: Absolute Process Yields

[redacted]

The reproducibility of chromatographic separation from lot-to-lot has been validated for [redacted] (6:127-131). Additionally, all in-process hold steps have been validated (6:132-185) and summarized (6:185).

The process has been validated for viral clearance following the ICH guideline for viral validation (7:1-36). During these studies it appears the [redacted] filtration device failed, resulting in a less that adequate viral reduction; these tests are to be repeated. Values for the viral clearance are summarized (7:29). *Results from the re-testing of the [redacted] viral removal step are provided in a supplement to the final BLA filing (2:2-7). All test specifications were meet.*

E. Reference Standards

Primary Reference Standard

TNFR:Fc was originally manufactured at the [redacted] scale in the Immunex facility in Seattle, WA. At that time a Bulk Drug Substance Reference Standard (3356-34) and a Drug Product Reference Standard (FXH0001) were both used for product testing. Upon scale-up [redacted] and transfer of TNFR:Fc manufacture to the [redacted] a new Reference Standard,

AZR-0003, was prepared(7:85-87, 90). This Reference Standard was [redacted] When the manufacturing process was scaled-up to the [redacted] scale a new Reference Standard, designated as 5577-003, was prepared from [redacted] scale material and qualified (7:88-89, 91-92). Between the time of qualification of the [redacted] scale **Reference Standard and the** [redacted] **scale Reference Standard, additional methods were introduced into the** Reference Standard qualification SOP along with refinement of specification limits. Reference Standard 5577-003 was used in testing the initial [redacted] scale product lots manufactured at [redacted] **has also qualified a Reference Standard derived from a single lot manufactured at the** [redacted] scale. This Reference Standard will be used for testing of commercial TNFR:Fc lots.

Qualification of the reference standard is described in SOP GG 10603

Testing for the qualification of the [redacted] reference standard included co-mixture analysis of both the [redacted] and [redacted] references. Data for this analysis did demonstrate that the two reference standards were chemically comparable (7:124-141). [redacted]

F. Specifications / Analytical Methods

1. Drug Substance Specifications and Tests

a. Specifications and Analytical Methods

Specifications for TNFR:Fc bulk solution ([redacted]) have been established (8:2-90, 91-100).

Procedure	Test Method	Specification

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Specifications for lot release tests are based on analysis of clinical and manufacturing experiences. Many specifications reflect historical / trend analysis of specific data sets. A comparison is made between Bulk Drug Substance Lot release tests and specifications for the validation lots and the commercial lots (8:95-97).

The majority of the SOP's and validation data provided in the BLA filling reflect procedures and data from ——— . Validation dates for the listed SOP's range from early 1997 through 1998. Many of the SOP's are on their second or third revision but no explanation is provided as to why or what the revisions were. Few of the validation studies used material from both the — scale (Immunex) and the — scale ——— . In only one case was reference made to a validated method at the — scale, which was transferred to ——— using a validated transfer protocol, and then validated at the — scale.

b. Certificates of analysis and Analytical Results

Certificates of analysis are included for the following ——— scale validation lots:

25001 (8:102-108) All tests were within specifications.
25002 (8:109-114) All tests were within specifications
25003 (8:115-120) All tests were within specifications
25005 (8:121-127) All tests were within specifications
25007 (8:128-132) All tests were within specifications

All test results were within specifications for lot release.

2. Impurities Profile

The process has been validated for the removal of impurities (6:110-126) (7:37-61)

G. Container / Closure System

Bulk Drug Substance (BDS) lots are stored in ——— tanks. The vessels are designed for controlled cooling and heating of the BDS by ——— The BDS is stored short term within the tanks at ——— or alternatively, the BDS is ——— for long term storage.

H. Drug Substance Stability

The stability of the drug substance at hold steps in the ——— processing have been studied and validated (6:132-185).

Real time stability data have been obtained which document the stability of TNFR:Fc Bulk Drug Substance manufactured at ——— 8:134-239). TNFR:Fc Bulk Drug Substance demonstrates biological and chemical stability for at least ——— when stored at ——— in representative ——— container.

TNFR:Fc Bulk Drug Substance may be stored in ——— containers at ——— Real time data support biological and chemical stability for at least ——— at this condition.

———

TNFR:Fc Bulk Drug Substance may be stored in ——— containers at ——— Real time data support biological and chemical stability for at least ——— at this condition.

Stability testing is ongoing.

III. Drug Product

A. Composition

The final dosage form of the product will contain lyophilized TNFR:Fc, at a concentration of either 25 mg/ vial or 10 mg/vial (11:2). Both product strengths contain the same excipient concentrations: Mannitol, USP (40 mg/vial); Sucrose, NF (10 mg/vial); Tromethamine ( ) and Water for Injection, USP (q.s. ad to 1.0 mL).

The diluent for ENBREL is Bacteriostatic Water for Injection (0.9% w/v Benzyl Alcohol (anti-microbial) in Water for Injection, USP) which will be obtained from a commercial source. *In a submission to the BLA the source of been identified as (2:31-68).* The pH of the final dosage forms is 7.4 ± 0.3 when reconstituted with 1.0 mL Sterile Bacteriostatic Water for Injection, USP.

B. Specifications and Methods for Drug Product Ingredients

Finished Drug Product consists of TNFR:Fc (10 mg/vial or 25 mg/vial), Tromethamine mannitol (present as a bulking agent for lyophilized cake) and sucrose (present as a cryoprotectant and glass forming gent). Fill volume is ~1mL/vial; the product is then lyophilized, stoppered and apped.

A tabular listing of excipients, grade and suppliers is provided (11:4), followed by accecptance tests and specifications for each excipient (11:5-8).

Tromethamine	USP/NF
Mannitol	USP/NF
Sucrose	USP/NF

C. Manufacturers

Immunex Corporation is employing the use of a contract manufacturer, , to manufacture TNFR:Fc Drug Product. The facility operates under cGMP conditions and has been licensed as a multi-product facility in the United States (License Number

Assembly, packaging and labeling of ENBREL will be done under contract by

D. Methods of Manufacture (11:49-87)

A flow chart has been provided which summarizes the formulation, full and finish process for the TNFR:Fc drug product (11:50-51). In general, the steps involved in the manufacture of the final drug product are:

1. Fill, lyophilization, capping and inspection of vials containing the drug product

2. Labeling, inspection and bulk packing of finished vials

3. Shipment of bulk packed drug product vials to the contract packager

4. Assembly of final commercial carton for distribution and sale. The final commercial carton (the "4-Pack") will contain four single-dose trays. Each preformed plastic tray will contain one labeled single-dose vial of either the — or 25 mg dosage form of TNFR:Fc and either a — or vial of product diluent (Bacteriostatic Water for Injection [0.9% benzyl alcohol], USP). The trays will be sealed with a paper label. In addition to the four dose trays, the 4-Pack Carton will contain one package insert and one or more copies of the patient package insert.

Batch records are included for the manufacture of a — Finished Drug Lot — and for the manufacture of a 25 mg/vial Finished Drug Lot (709685) (16:1-end). These lots were filled using the existing — filling equipment. Batch records for lots filled using the new — equipment will be submitted in a separate filing.

E. Specifications and Test Methods for Drug Product

1. Sampling Procedures

No SOP is referenced concerning sampling procedure. In the submission, Immunex states that "Sample vials are selected from the — of the batch. A defined number of vials are kept in the department of pharmaceutical production at — as retain samples. Sample vials for testing are delivered to the department of biotech production and distributed to the analytical laboratories for analytical testing, microbiological testing, or sterility testing.".

2. Specifications and Methods

Test methods and specifications for release of TNFR:Fc are defined for both the — (SOP QA 10311) and the 25 mg dosage form (SOP QA 10312). Lot release tests and their specifications are summarized (11:89-163).

Procedure	Test Method	Acceptance Criteria
—	QA10222 SQP(20:133-140) VAL(19:152-153)	—

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)

Procedure	Test Method	Acceptance Criteria
QA10222 SOP(20:133-140) VAL(19:152-163)		
QA10315 SOP(20:67-70) VAL(18:8-15)		
QA10316 SOP(20:63-66) VAL(18:16-30)		
QA10340 SOP(20:46-51) VAL(19:164-177)		
QA10337 SOP(52-55)		
QA10302 SOP(20:94-98) VAL(19:37079)		
QA10309 SOP(20:71-77) VAL(18:169-196)		
QA 10317 SOP(20:56-62) VAL(19:178-182)		
QA10294 SOP(20:114-118) VAL(18:31-39)		
QA10375 SOP(20:36-45) VAL(18:148-168)		
QA10178 SOP(20:146-153) VAL(18:50-63)		

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)

Procedure	Test Method	Acceptance Criteria
QA10175 SOP(20:154-162) VAL(18:40-49)		
QA1022[illegible] SOP(20:85-93) VAL(19:12-23)		
007/97 SOP(20:2-6) VAL(19:183-187)		
008/97 SOP(20:7-11) VAL(19:183-187)		

Specifications for lot release tests are based on analysis of clinical and manufacturing experiences. Many specifications reflect historical / trend analysis of specific data sets. A comparison is made of Bulk Drug Substance Lot release tests and specifications for the validation lots and the commercial lots (12:5-6).

3. Certificates of Analysis and Analytical Results

Testing of finished drug product (12:1-11) and certificates of analysis (12:12-45) are included for the following finished Drug Product Lots:

25 mg/vial Lot # FFM-709581 (From BDS Lot 25003)
Lot # FFM-709685 (From BDS Lot 25005)

All test results were within specifications for lot release.

F. Container / Closure System

TNFR:Fc Drug product is delivered to a

G. Drug Product Stability

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)

The TNFR:Fc Lyophilized Drug Product stability studies include vials stored at [redacted] The [redacted] stability studies are bracketed by a study ([redacted]) and by [redacted] to provide an indication of accelerated stability behavior.

Stability tests and acceptance criteria (13:1-180) are summarized as follows:

Stability Procedure	Stability Test Method	Stability Acceptance Criteria
Quality		
[redacted]	QA10222 SOP(20:133-140) VAL(19:152-163)	[redacted]
[redacted]	QA10222 SOP(20:133-140) VAL(19:152-163)	[redacted]
[redacted]	QA10315 SOP(20:67-70) VAL(18:8-15)	[redacted]
[redacted]	QA10316 SOP(20:63-66) VAL(18:16-30)	[redacted]
[redacted]	QA10340 SOP(20:46-51) VAL(19:164-177)	[redacted]
[redacted]	QA10302 SOP(20:94-98) VAL(19:37079)	[redacted]
[redacted]	QA10309 SOP(20:71-77) VAL(18:169-196)	[redacted]
[redacted]	QA10317 SOP(20:56-62) VAL(19:178-182)	[redacted]
[redacted]		
[redacted]	QA10294 SOP(20:114-118) VAL(18:31-39)	[redacted]
[redacted]		
[redacted]	QA10375 SOP(20:36-45) VAL(18:148-168)	[redacted]
[redacted]		
[redacted]	QA10178 SOP(20:146-153) VAL(18:50-63)	[redacted]

Abbreviations: Standard Operating Procedure (SOP), Validation Report (VAL)
References to the BLA volumes are in the format Volume: page, e.g. (8:99-124)

	QA10175 SOP(20:154-162) VAL(18:40-49)	
Safety		
	008/97 SOP(20:7-11) VAL(19:183-187)	Meets USP requirements

In addition to the formal specifications listed above, Drug Product stability is being gathered "for information only" on the and the 25 mg qualification lots for analysis.

Stability studies have been completed through the 6-month timepoints for the TNFR:Fc Lyophilized Drug Product, produced as and 25 mg dose vials that have been filled at using a vial with a stopper. The data provided indicates that the Drug Product is stable and passes all tests specifications through six months (13:63-177). One additional lot of the 25 mg dosage form was placed on the stability program in January 1998 and will be included in future stability reports. Real time stability data have been obtained which document the stability of TNFR:Fc Lyophilized Drug Product, and 25 mg dose vials. The and 25 mg dose vials of TNFR:Fc Lyophilized Drug Product produced at the scale, demonstrate biological and chemical stability for at least six months when stored at

Stability data will be updated to include the 12 month time point.

Supportive stability data for up to 48 months is provided for Formulated Drug Product produced at either Immunex (, and and filled at (14:1-188).

IV. Investigational Product / Formulation

A. Process Changes due to Scale-up (17:1-26)

TNFR:Fc used for pivotal clinical trials was produced at the Immunex The production stage of the cell culture process has a final working volume of approximately , nominally the Immunex scale. The Bulk Drug Substance was transferred to a contract fill/finish facility, where the final compounding and lyophilization was conducted.

Commercial manufacture of TNFR:Fc is conducted at the cell culture manufacturing facility in This site was selected based on the availability of large scale production capacity and resident technical expertise with large scale mammalian cell culture processes. The selected production scale at this site is nominally Lyophilization of the drug

product is also performed at [redacted]. The [redacted] site is currently licensed by the FDA for production of biologics for human therapeutic use.

The Immunex [redacted] TNFR:Fc manufacturing process was transferred to [redacted] and scaled-up to [redacted] during 1996 and 1997. The Immunex [redacted] TNFR process was initially conducted at the [redacted] scale at [redacted]. Process runs at this scale were valuable in demonstrating equipment function, correct and adequate raw materials supply, and overall process performance. Additionally, some process improvements were identified during this phase. No investigational drug was produced at the [redacted] scale and this was not intended as the commercial scale, but rather, a logical progression to the [redacted] commercial scale.

Subsequent to the [redacted] runs, the process was scaled up approximately [redacted] to an approximate [redacted] final working volume. The resultant manufacturing process is essentially a direct scale-up of the Immunex [redacted] TNFR:Fc process with minimal changes.

1. Cell culture process changes made to accommodate the [redacted] scale were:

a. The [redacted] cell culture process employs a [redacted] at all [redacted] steps due to observed [redacted]. The process calls for [redacted] for the [redacted] inoculum stages and [redacted] for the [redacted] and [redacted] production stages, added as necessary to control [redacted]. This measure was employed to improve process robustness by reducing the chance for exhaust vent filter fouling. The Immunex [redacted] cell culture process does not employ the use of

b. A provision for the addition of supplemental [redacted] as necessary, has been included for the [redacted] production stage. This was done as a proactive measure to add robustness to the process due to the detrimental effect of [redacted] depletion on culture health. The Immunex [redacted] production stage batch record does not have this provision.

c. For the [redacted] cell culture harvest/ [redacted] stage, due to practical difference in scale [redacted] management), the culture broth is concentrated by [redacted] approximately [redacted] compared to approximately [redacted] by [redacted] in the Immunex [redacted] process. Additionally, the [redacted] operation is conducted at a culture broth temperature of approximately [redacted] compared to the Immunex [redacted] [redacted] operation at less than [redacted]. This measure was taken to provide a more consistent and robust [redacted] unit operation.

d. The TNFR:Fc [redacted] filtrate is further [redacted] using [redacted] filters prior to the next unit operation. The [redacted] process supplements the filters employed at Immunex with either [redacted] filters which have a high load capacity and prevent fouling of the subsequent filters. This has been employed to ensure a more reliable and consistent [redacted] process.

e. The [redacted] and initial [redacted] are conducted as discreet unit operations. The Immunex [redacted] process combines the [redacted] operations in a [redacted] fashion due solely to tank capacity limitations, i.e., the Immunex [redacted] Due to the separation of these unit operations at [redacted] the [redacted] broth is [redacted] filtered and stored at [redacted] for up to [redacted] until the [redacted] unit operation.

2. Purification process modifications to accommodate the scaled-up process include:

a. As described above, the [redacted] operation performed subsequent to broth [redacted] has been separated from the combined method employed with the Immunex [redacted] process. The [redacted] purification process employs [redacted] molecular weight [redacted] membrane compared to the [redacted] molecular weight [redacted] used in the Immunex [redacted] process. This change was based on [redacted] experience with the [redacted] and demonstration of comparable performance at both the [redacted] and [redacted] scales. Additionally, the initial buffer exchange has been increased from [redacted] to [redacted] This has been changed to ensure a more complete buffer exchange and to provide additional removal of cell culture medium constituents prior to the first chromatography step.

b. Both the Immunex [redacted] and the [redacted] process employ [redacted] In the Immunex [redacted] process the pooled [redacted] eluants undergo an approximately [redacted] followed by an approximately [redacted] with water for injection, via [redacted] using [redacted] As a viral inactivation step, the pool is then adjusted to approximately pH [redacted] and held for [redacted] The [redacted] process differs in that each [redacted] cycle sublot is [redacted] and subjected to the [redacted] Additionally, the viral inactivation step differs in that the pH is approximately [redacted] and the incubation time is increased from [redacted] hours. This change to the viral inactivation method has been demonstrated to provide an equivalent level of viral inactivation while reducing the amount of TNFR:Fc aggregation, thereby improving product quality

c. For ——— column sanitization and regeneration Immunex employs ——— and ———, respectively. ——— employs ——— and ——— for these steps.

d. The Immunex ——— process follows viral inactivation with ——— chromatography. With the ——— process the individually treated eluants are first pooled, then concentrated ——— and diluted approximately ——— via ——— molecular weight). The ——— process then proceeds to the ——— chromatography step.

e. Sanitation and regeneration of the ——— resin differs between the two process scales in that the ——— process employs a more vigorous regeneration protocol for ——— removal. The Immunex ——— process sanitizes the column with ———, regenerates with ——— ——— and stores in ———. The ——— process sanitizes/regenerates the column with ——— and ——— and stores in ———

f. The ——— process incorporates virus removal filtration via the ——— filter product. This filtration results in additional viral clearance, achieved via ——— The Immunex ——— process does not employ this operation.

3. The final formulations of each process are identical, however the formulation methodology has minor differences. The Immunex ——— process employs ——— perform a ——— buffer exchange into ——— buffer followed by concentration to approximately ——— TNFR:Fc. At Immunex the ——— buffer utilizes ——— The Bulk Drug Substance is stored in ——— ——— bottles and transferred to a contract filling site at which point the TNFR:Fc is diluted in a ——— vessel to either ——— or 25 mg/mL in the ——— buffer and filled immediately. The ——— process material employs the same ——— but the ——— is performed with the ——— buffer and the concentration is adjusted directly to 25 mg/mL TNFR:Fc and stored at ——— in a ——— vessel until filling. From this point the material may be filled or ——— ——— At ——— the ——— buffer utilizes the proper ratio of ——— to achieve the specified pH.

4. The Immunex ——— lyophilized product container-closure system employs a ——— vial while the ——— process employs a ——— vial. The smaller vial size was selected in order to accommodate a larger number of vials per lyophilization run. As a result, capacity increased from approximately ——— units to ——— units. Because of the smaller vial size, and no change in target fill volume, the depth of the

solution and subsequent cake thickness in the — vial increased by approximately —percent. Development runs demonstrated that this had minimal effect on the overall lyophilization cycle, as primary and secondary drying times remain the same at approximately———————, respectively. Moisture and reconstitution times are comparable for both configurations.

B. Comparability testing and Data

Determinations of product comparability were based on a combination of analytical testing, *in vitro* biological assays, and assessment of pharmacokinetics in both a —— model and a ———————— model. The criteria for demonstration of comparability were predefined and the acceptance criteria were predetermined prior to testing the ——— material. These criteria were identical to or more stringent than the specifications for the — scale material that were in use at the time the comparability testing was performed (17:27-67). In cases where new assays were used, such as ———————— the acceptance criteria was specified as comparable to Reference Standard (i.e. ———————— or —— of Reference Standard (i.e. ——— . A human bioequivalence study has also been conducted.

The data presented demonstrates comparability between the material produced at Immunex (—) and the material produced at ————————. However, the most convincing data to demonstrate comparibality is the ——— analysis. This analysis will be performed on the new reference material from ———————— scale and the reference material from Immunex, ——scale (7:97-99). This data has not been submitted for review.

C. Comparability Protocols

Comparability protocols have been prepared for potential changes in the manufacture of TNFR:Fc, including changes in cell culture production, purification, manufacture of drug product, analytical methods, packaging, distribution and facilities (20:163-190). Changes made will follow existing change control procedures including an appropriate evaluation of the change, and validation to ensure the change does not adversely affect the performance of the process or the quality of the product. The comparability protocols included define the type of potential change and the corresponding reporting category (supplement submission at least 30 days prior to distribution of the product made using the change or Annual Report), as well as identify the general acceptance criteria and standards that changes must meet in order for the change to be approved. The intent of the enclosed comparability protocols is to define the evaluation procedures, acceptance criteria and regulatory reporting requirement that Immunex will use when executing a manufacturing change.

[redacted]

Additionally, the flow chart provided to document possible [redacted] *in more indicative of* [redacted] *A validated SOP for* [redacted] *needs to be submitted for review.*

[redacted]

V. Questions and comments:

1. There is no specification mentioned for the shelf life of the ——— column, the ——— column or the filters. No mention is made of the number of times the columns and filters may be used (no validation data presented). A comment is made by Immunex that validation data for the

After review of the column reuse validation data provided May 7, 1998 I have the following comments:

A. It is unclear if the ——— column is packed once and used to a validated limit, or if the column is disassembled and repacked as needed; this point requires clarification. In the supplemental volume, Immunex indicates that ~ resin from the production scale (runs 25000-25007, ——— was packed into a ——— column to finish validation of ——— (2;8). There is no indication that it is an established protocol to breech column integrity to sample resin; ———

THIS PAGE WAS DETERMINED TO BE NOT RESPONSIVE TO YOUR REQUEST

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